REMARKS

This paper is being filed in Response to the Officer Action mailed May 4, 2007. Applicants respectfully request reconsideration of the application.

Regarding the Claim Amendment

Claim 1 has been amended to recite that the lytic peptide "consists of" from 10 to 39 amino acid residues. The amendment is supported, for example, at page 36, lines 20-21; and at page 41, lines 9-10. Thus, as the amendment to claim 1 is supported by the specification, no new matter is added and entry thereof is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph, Written Description

The rejection of claims 1 to 8, 11 to 14, 17, 127 and 131 to 133 under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. The grounds for rejection are as set forth on pages 4-8, and appear to be due to allegedly insufficient information regarding "identifying characteristics" of hormone analogues and lytic peptides, or acute phase responsive promoter, transposase and transposon insertion sequences.

A proper analysis for written description under 35 U.S.C. §112, first paragraph, is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). In order to satisfy the written description requirement, "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976). Furthermore, the Federal Circuit held "that (1) examples are not necessary to support adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). Thus, an adequate written description of a genus can be satisfied in a variety of ways that do not require disclosure of specific examples, an actual reduction to practice, or a known structure.

Possession, may be show by a variety of ways, including description of actual reduction to practice, or by showing that the invention was ready for patenting, such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show Applicants was in possession of the claims invention. *Citations omitted.* For example, a "description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus *or* of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559,1568 (Fed. Cir. 1997), emphasis added. Thus, the written description requirement can be satisfied solely by a description of a representative number of species falling within the genus even without reciting structural features common to the members of the genus.

In terms of the number of species adequate to represent a species, although courts have not specified the minimum number of species, "every species in a genus need not be described in order that a genus meet the written description requirement." *Id.* (citing *Utter v. Hiraga*, 845 F.2d 993, 998-99 (Fed. Cir. 1988) Even in an unpredictable art an adequate written description does not require disclosure of every species encompassed by the claims. *In re Angstadt*, 537 F.2d 498,502-3 (CCPA 1976) Thus, a description of each and every hormone analogue or lytic peptide species is not required to satisfy the written description requirement.

Here, the written description requirement is clearly satisfied in view of the fact that a large number of hormone analogues and lytic peptide species, sufficient in number to represent a genus, is disclosed in the specification. Furthermore, the large number of hormone analogues each of which has a characteristic structure, means that structural features shared among the members of the genus are described. Moreover, the lytic peptide portion is expressly defined in structural terms in the claims, namely by 1) length (10 to 39 amino acids); 2) charge (basic); and 3) form an amphipathic alpha helix.

In terms of hormone analogs, the specification discloses analogs of hormones. In particular, for example, the specification discloses GnRH analogues, such as substitutions at the 6 and 10 positions of GnRH that produce superagonists with greater affinity for GnRH receptor (page 12, line 28, to page 13, line 3). The specification also discloses that the initial

pyro glutamic acid residue of GnRH of a fusion peptide could be substituted with glutamine (page 13, lines 24-27).

In addition to the guidance in the specification, as acknowledged by the Examiner, a large number of hormone analogs were known in the art at the time of the invention. Given the large number of hormone analogs, such analogs are adequately described.

As evidence that analogs of gonadotropin releasing hormone (GnRH), also known as luteinizing hormone releasing hormone (LHRH), were known in the art, Applicants direct the Examiner's attention to several publications that describe analogs of GnRH. In particular, Sealfon *et al.* (*Endocrine Reviews*, 18:180 (1997)) is a review article that, among other things, discusses the apparent role of each of the individual amino acids in the GnRH decapeptide, and describes the types of substitutions that may be made in analogs (see particularly pp. 184-191, and Fig. 8 on page 190). The paper authored by Karten *et al.* (*Endocrine Reviews*, 7:44 (1986)) describes or includes citations to over 2000 GnRH analogs (p. 44, par. 1) that had been synthesized and characterized. The paper authored by Sealfon *et al.* (*Human Reproduction Update*, 1:216 (1995)) is a review of GnRH receptor structure and regulation of receptor expression which mentions that thousands of GnRH analogs have been synthesized and studied (p. 216). The paper authored by Filicori (*Drugs*, 48:41 (1994)) is a review article discussing GnRH agonists, and examples of the types of modifications that may made, such as the substitution of the sixth amino acid residue (glycine), which have higher receptor affinity. Another review article is Conn *et al.* (*New Engl. J Med*, 324:93 (1991)), which describes several GnRH analogs. The paper authored by Nechushtan *et al.* (*J Biol. Chem.*, 298:11597 (1997)) describes a GnRH analog in which tryptophan replaced glycine as the sixth amino acid. In view of the fact that numerous analogs of GnRH were known in the art, GnRH analogs are adequately described.

As evidence that analogs of luteinizing hormone and chorionic gonadotropin were known in the art, Applicants direct the Examiner's attention to several publications that describe analogs of luteinizing hormone and chorionic gonadotropin. In particular, Morbeck *et al.* (*Molecular & Cellular Endocrinology*, 97:173 (1993)) describes studies used to identify all linear regions that participate in the binding of hormone to receptor. The most potent inhibitor in a competitive binding assay was a peptide containing residues 81-95 of hCG. Peptides were prepared in which each residue of the 81-95 hCG sequence was sequentially replaced by alanine, to identify the residues important for binding. Five such residues were

identified. In addition to describing the 81-95 hCG analog, this reference provides guidance to the skilled artisan to design other analogs of the beta subunit of luteinizing hormone or of chorionic gonadotropin. The paper authored by Garcia-Campayo *et al.* (*Nature Biotechnol.*, 15:663 (1997)) describes a luteinizing hormone analog, in which the α and β subunits were fused through a linker, which was active and had greater *in vitro* stability than the native heterodimer. The paper authored by Sugahara *et al.* (*Proc. Natl. Acad. Sci. USA*, 92:2041 (1995)) describes a fusion of human chorionic gonadotropin α and β subunits which had increased activity both *in vitro* and *in vivo*. The paper authored by Puett *et al.* (*Biol. Repro.*, 58:1337 (1998)) is a review concerning human chorionic gonadotropin and analogs. The paper authored by Han *et al.* (*Mol. Cell. Endocrin.*, 124:151 (1996)) describes several analogs of LH with amino acid substitutions in the beta subunit, as well as numerous specifically described mutations which provides guidance to one of skill in the art in designing other analogs. The paper authored by Zalesky *et al.* (*J. Anim. Sci.*, 70:3851 (1992)) describes thirteen isoforms of LH, each of which could be considered an LH analog. The chapter authored by Hartee (Multiple forms of pituitary and placental gonadotropins," pp. 147-154 in S. Milligan (Ed.), *Oxford Reviews of Reproductive Biology* (1989)) describes variants of FSH, LH, and CG, such as seven isoforms of LH and six isoforms of hCG which all had activity *in vivo*. In view of the fact that numerous analogs of luteinizing hormone and chorionic gonadotropin were known in the art, luteinizing hormone and chorionic gonadotropin analogs are adequately described.

As evidence that analogs of follicle stimulating hormone (FSH) were known in the art, Applicants direct the Examiner's attention to publications that describe FSH analogs. In particular, Grasso *et al.* (*Endocrinol.*, 137:5370 (1996)) describes a synthetic tetrapeptide amide analog to the beta subunit of FSH. The paper authored by Dias *et al.* (*Biol. Repro.*, 58:1331 (1998)) is a review concerning human FSH, which describes structure-activity relationships, FSH analogs, synthetic peptides, site-directed mutagenesis, and the role of specific amino acid residues. The paper authored by Cerpa-Poljak (*Endocrinol.*, 132:351 (1993)) discloses t several isoforms of human recombinant FSH, each of which can be considered an FSH analog. In view of the fact that numerous analogs of follicle stimulating hormone (FSH) were known in the art, FSH analogs are adequately described.

As evidence that analogs of melanocyte-stimulating hormone were known in the art, Applicants direct the Examiner's attention to a publication that describes melanocyte-

stimulating hormone analogs. In particular, Goldman *et al.* (*Endocrinol.*, 112:435 (1983)) describes two MSH analogs: desacetyl aMSH; and *N O*-diacetyl αMSH. In view of the fact that analogs of melanocyte-stimulating hormone were known in the art, melanocyte-stimulating hormone analogs are adequately described.

As evidence that analogs of somatostatin were known in the art, Applicants direct the Examiner's attention to a publication that describes somatostatin analogs. In particular, Patel *et al.* (*Endocrinol.*, 135:2814 (1994)) reports a study of 32 different somatostatin analogs. Two of the somatostatin analogs, SMS 201-995 and BIM 23014, were in clinical use as of 1994. References to other papers describing somatostatin analogs, as well as commercial sources for particular somatostatin analogs, are also mentioned. An editorial authored by Berelowitz (*Endocrinol.*, 136:3695 (1995)) reported that as of 1995 "a large number of analogs [of somatostatin] with improved stability in plasma" had been synthesized; and also that one, octotreotide, was commercially available, and that two others, lanreotide and somatuline, were in clinical trials. In view of the fact that somatostatin analogs were known in the art, somatostatin analogs are adequately described.

In sum, numerous analogs of the specific hormones recited in the claims were known in the art at the time of the invention. Accordingly, one skilled in the art would be apprised of a representative number of hormone analogs of the specifically recited hormones.

In terms of lytic peptides, Applicants first wish to address the Examiner's concern regarding the importance of helix formation (pages 5 and 8 of the Office Action). In this regard, claim 1 recites that the lytic peptide "will form an amphipathic alpha helix." Thus, in view of the fact that the claimed genes encode peptides in which the lytic peptide will form an amphipathic alpha helix, the grounds for rejection due to non-helical peptides is not relevant since non-helical lytic peptides are not encoded by the claimed genes.

The specification discloses lytic peptide species hecate. The specification also discloses structural features of peptides that have lytic activity. For example, the specification discloses amphipathic alpha helix (see, for example, page 36, line 18-22). Furthermore, the specification discloses substitutions compatible with lytic activity. For example, the specification discloses amino acids that preserve the amphipathic nature of the peptides (e.g., replacing a polar residue with another polar residue, or a non-polar residue with another non-polar residue), substitutions that preserve charge distribution (e.g., replacing an acidic residue with another acidic residue, or a basic residue with another basic residue),

or lengthening or shortening the amino acid sequence while preserving its amphipathic character or charge distribution (page 37, lines 5-10). Thus, in view of the guidance in the specification the skilled artisan would know that 1) preserving amphipathic structure and charge distribution of lytic peptides is important to activity; and 2) which amino acid substitutions and deletions would be compatible with amphipathic character and charge distribution and, therefore the amino acid substitutions and deletions that would maintain at least partial lytic peptide activity. In view of this knowledge, clearly the skilled artisan would know of a number of variants peptide that would have at least partial lytic peptide activity.

Moreover, the lytic peptide portion is defined structurally in the claims, namely by length, charge and an amphipathic alpha helix. The recitation of length, charge and an amphipathic alpha helix are all structural features common to lytic peptides.

In sum, in view of the guidance in the specification and knowledge in the art at the time of the invention of numerous hormone analogs, as well as the guidance regarding structural features important for lytic peptide activity and the recitation of structural features common to lytic peptides in the claims, the skilled artisan would be apprised of a representative number of hormone analogs and lytic peptides. As such, an adequate written description of claims 1 to 8, 11 to 14, 17, 127 and 131 to 133 is provided, and Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description be withdrawn.

Rejection under 35 U.S.C. §112, First Paragraph, Enablement

The rejection of claims 1 to 8, 11 to 14, 17, 127 and 131 to 133 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. The grounds for rejection are as set forth on pages 8-13, and appear to be due to allegedly insufficient information regarding "identifying characteristics" of hormone analogues and lytic peptides, promoters (acute phase responsive promoter), transposon insertion sequences and transposon genes.

The proper standard for enablement under 35 U.S.C. §112, is whether one skilled in the art could make and use the invention without undue experimentation. In this regard, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the

direction in which the experimentation should proceed." *In re Wands* 858 F.2d 731, 737 (Fed. Cir. 1988)

Applicants first wish to point out that the claims are directed to genes. Thus, a proper analysis for enablement of the claims would be whether it would require undue experimentation to make and use the genes, not whether it would require undue experimentation to make and use the peptides. In this regard, except for promoters (acute phase responsive promoter), transposon insertion sequences and transposon genes, all grounds for rejection set forth in the Office Action relate to making and using the peptides, not the genes. Consequently, the grounds for rejection set forth in the Office Action relating to making and using peptides are not relevant to the claims.

In regard to making and using the claimed genes, Applicants respectfully point out those producing genes by recombinant methods was routine and well within the capability of one skilled in the art at the time of the invention. Thus, if the skilled artisan wished to make genes that encode peptide variants undue experimentation would not be required. Furthermore, the claimed genes could be expressed in cells in order to produce encoded peptide using a cell based expression system or in vitro translation system to produce peptide variants. Thus, if the skilled artisan wished to use the claimed genes to produce peptide variants undue experimentation would not be required. Consequently, the claims are adequately enabled under 35 U.S.C. §112, first paragraph.

Moreover, although not required to enable the claimed genes, if desired, peptide variants encoded by the claimed genes could be readily screened for activity using a routine cell lysis assay. For example, the specification discloses several in vitro cell lysis assays to determine activity of peptides (see, for example, pages 21-23, Examples 24-31 and 32-33; and pages 33-34, Examples 52-58). Thus, undue experimentation would not be required to identify peptide variants encoded by the claimed genes that had activity.

Similar to identifying peptide variants, activity of a promoter (e.g., an acute phase responsive promoter), transposon insertion sequence, and transposon gene can be determined using routine assays well within the capability of one skilled in the art at the time of the invention. Thus, undue experimentation would not be required to identify promoters (e.g., an acute phase responsive promoter), transposon insertion sequences, and transposon genes that had activity.

Analogous to *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988), where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a

particular binding characteristic did not require undue experimentation, undue experimentation would not be required to identify peptide variants that have activity, given that 1) producing peptides was routine in the art at the time of the invention; and 2) cell death assays were routine in the art at the time of the invention. Likewise, undue experimentation would not be required to identify promoters, transposon insertion sequences, and transposon genes that have activity, given that assays for determining such activities were known in the art at the time of the invention. Consequently, the skilled artisan need not "predict" in advance genes that encode peptide variants or promoters, transposon insertion sequences and transposon genes that have activity. Instead, the skilled artisan would merely screen peptide variants or promoters and transposon insertion sequences using an appropriate activity assay.

In view of the foregoing, the skilled artisan could readily produce genes that encode peptide variants, and promoters, transposon insertion sequences and transposon genes that have activity without knowing *a priori* the effect of a particular substitution or deletion without undue experimentation. Consequently, claims 1 to 8, 11 to 14, 17, 127 and 131 to 133 are adequately enabled under 35 U.S.C. §112, first paragraph, and Applicants respectfully request that the rejection be withdrawn.

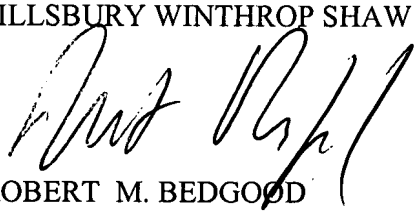
CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1 to 8, 11 to 14, 17, 127 and 131 to 133 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065. Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

PILLSBURY WINTHROP SHAW PITTMAN LLP



ROBERT M. BEDGOOD
Reg. No. 43488
Tel. No. 858.509.4065
Fax No. 858 509.4010

Date: November 5, 2007
12255 El Camino Real
Suite 300
San Diego, CA 92130-4088
(619) 234-5000